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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/078,927	02/19/2002	Thomas Curran	SJ-01-0032	6357

28258 7590 06/19/2008

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EXAMINER	
STEADMAN, DAVID J	
ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
06/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/078,927	CURRAN ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,10,11,13-15 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8,10,11,13-15 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

[1] Claims 4-8, 10-11, 13-15, and 36-38 are pending in the application.

[2] Applicant's amendment to the claims, filed on 4/17/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. Claims 1, 32, 35, and 39-40 have been canceled and claims 4-8, 10-11, and 37-38 have been amended relative to the claim listing filed on 11/1/07.

[3] Applicant's amendment to the specification, filed on 4/17/08, is acknowledged.

[4] Applicant's arguments filed on 4/17/08 in response to the Office action mailed on 1/25/08 are acknowledged. Applicant's arguments have been fully considered and are deemed to be persuasive to overcome some of the rejections and/or objections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

[5] The text of those sections of Title 35 U.S. Code not included in the instant action can be found in a prior Office action.

Specification/Informalities

[6] The objection to the specification as introducing new matter by way of the specification amendments filed on 4/25/2005 and 11/21/2005 is maintained for the reasons of record and the reasons stated below. The objection was fully explained in a prior Office action. See particularly paragraph 6 beginning at p. 3 of the Office action mailed on 8/6/07.

RESPONSE TO ARGUMENT: At p. 5 of the instant remarks, applicant argues the objection has been rendered moot by amendment to the specification.

Applicant's argument is not found persuasive. The specification amendment filed on 11/21/05 introduced a sequence listing computer readable form and paper copy with SEQ ID NO:4 and 5 that find no descriptive support in the application as filed. Accordingly, the objection is maintained.

Claim Objection

[7] The objections to claims 11 and 37 are withdrawn in view of the instant claim amendment.

Claim Rejections - 35 USC § 112, First Paragraph

[8] The scope of enablement rejection of claims 36, 38, and 40 under 35 U.S.C. 112, first paragraph, is withdrawn upon further consideration of the rejection and in view of applicant's remarks filed on 4/17/08.

Applicant notes the specification defines the term "candidate sequence" and further notes that "In the present invention, only serines 491 and 515 in the carboxy region of murine and human Dab1 fall within the definition of a serine within a candidate sequence…as claimed and described in the specification" (remarks, paragraph bridging pp. 6-7). According to the instant specification, a "candidate sequence" is defined as "a sequence of amino acids which contains a serine followed by a proline in +1 position and a lysine in +3 position, the serine being a preferred site for Cdk5 activity (Songyang

et al., Mol Cell Biol, 16:6486-6493, 1996)" (p. 5, lines 1-3). According to MPEP 2111.01.IV, "Where an explicit definition is provided by the applicant for a term, that definition will control interpretation of the term as it is used in the claim. *Toro Co. v. White Consolidated Industries Inc.*, 199 F.3d 1295, 1301, 53 USPQ2d 1065, 1069 (Fed. Cir. 1999)". Claim 36 recites "determining whether the carboxy terminal domain…is phosphorylated on a serine within a candidate sequence" and claim 38 requires "Each of claims 36 and 38 recites "detecting binding of the phosphoantibody to a serine within a candidate sequence in the carboxy terminal domain of Dab1".

Claim Rejections - 35 USC § 103

[9] Claim(s) 4-8 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curran et al. (US Patent 6,323,177; "Curran") in view of Keshvara et al. (*J. Biol. Chem.* 276:16008-16014, 2001; cited as reference AG2 in the IDS filed on 3/25/02; "Keshvara"), Niethammer et al. (*Neuron* 28:697-711, 2000; cited as reference AM1 in the IDS filed on 3/25/02; "Niethammer"), Carr et al. (*Analytical Biochem.* 239:180-192, 1996; "Carr"), and GenBank Accession Numbers 1771281 and 3288851. It is noted that due to an inadvertent editing error, claims 4-5 were omitted from the prior art rejections as set forth in the prior Office action. Claims 4-5 have been included herein and the instant Office action is made non-final. The examiner regrets any inconvenience due to this oversight.

The claims are drawn to methods of detecting Cdk5 serine kinase activity in a biological sample, by determining whether Dab1 is phosphorylated on a serine residue.

The reference of Curran teaches "In vitro cdk5 can also phosphorylate Dab1 on serine residues" (column 4, lines 46-47) and "In particular, identification of the site of Dab1 phosphorylation may permit its use as a potential target for agonists and antagonists. Cdk5 phosphorylates Dab1 in vitro. We can screen for inhibitors and agonists of this activity in connection with Reelin binding to VLDLR, and map the phosphorylation sites. Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. Thus, this area of exploration has significant relevance" (column 23, line 63 to column 24, line 4). Curran does not teach those residues of Dab1 that are phosphorylated by Cdk5; does not teach Dab1 is phosphorylated in biological sample, *e.g.,* brain and blood, from a mouse or human; and does not teach methods of measuring Cdk5 activity by determining whether or not Dab1 is phosphorylated at these residues.

The references of Niethammer, Keshvara, and Carr are cited as showing various methods for analysis of a phosphoprotein. It is noted that Carr was not included in the rejection under 35 U.S.C. 103(a) as set forth in the prior Office action, but is included herein to demonstrate the broad range of techniques available to identify a site of phosphorylation in a polypeptide. Niethammer teaches a method for determining the sites of phosphorylation of a substrate polypeptide of Cdk5, NUDEL. For example, the method involves immunoprecipitation of the substrate polypeptide from mouse brain extracts with or without catalytically active Cdk5 activity and determining whether or not the substrate protein has altered electrophoretic mobility (p. 704, Figures 7A, 7D, and 7E and p. 709, column 1); teaches identifying those amino acids that are potentially

phosphorylated by Cdk5 kinase in the primary sequence of the polypeptide, which have serine-proline (p. 703, column 2, bottom and p. 698, Figure 1A); individually and combinatorially mutating the potential Cdk5-phosphorylated serine or threonine residue to an alanine; and comparing the electrophoretic mobility shift in migration of immunoprecipitated wild-type and mutant proteins in the presence and absence of catalytically active Cdk5 in COS7 cells; and identifying those residues that are phosphorylated by Cdk5 by comparing the Cdk5 phosphorylation of the wild-type, individual mutants, and combinatorial mutants (p. 704, Figure 7F and p. 708, column 1 to p. 709, column 2).

The reference of Keshvara teaches a method of identifying sites of tyrosine phosphorylation of Dab1 by Src, using a method similar to that of Niethammer, wherein the tyrosine residues phosphorylated by Src are identified by mutating each potential Src-phosphorylated tyrosine to phenylalanine and analyzed by autoradiography and tryptic phosphopeptide analysis (p. 16009, Figure 1A-B and column 1 under *Kinase Reactions* and *Phosphopeptide Mapping;* p. 16010, Figure 2A-B). Keshvara teaches an expression vector encoding Dab1 for use in expressing Dab1 in a eukaryotic cell (p. 16009, under *Cell Culture and Immunoprecipitations*).

Carr teaches a method for detecting and sequencing phosphopeptides from an enzymatic digest of a phosphoprotein by mass spectrometry (p. 180, abstract).

GenBank Accession Numbers 1771281 and 3288851 disclose the amino acid sequences of murine Dab1 and human Dab1, respectively. Given these sequences at the time of the invention, a skilled artisan would have recognized that by visually

inspecting the amino acid sequences of murine and human Dab1 as shown by GenBank Accession Numbers 1771281 and 3288851, respectively, five potential Cdk5 serine-proline phosphorylation sites (as noted by Niethammer) are present at positions 260, 400, 481, 491, and 515.

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851 to immunoprecipitate Dab1 from mouse brain extract with and without catalytically active Cdk5 and analyze its electrophoretic mobility and to determine whether or not serine at position 260, 400, 481, 491, and 515 are phosphorylated by mutating Dab1 serines at positions 260, 400, 481, 491, and 515 to alanine, individually and combinatorially, and determining the serine(s) that is/are phosphorylated by Cdk5 in accordance with the methodology of Niethammer and Keshvara. Alternatively, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of Curran, Keshvara, and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to determine its potential site(s) of phosphorylation according to the method of Carr. By doing this, one of ordinary skill in the art would have practiced the active method step(s) as recited in the claims. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates serines of Dab1, the sites of Cdk5 phosphorylation of Dab1 can be identified, and may have "significant relevance" to screen for agonists and antagonists because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD.

One would have had a reasonable expectation of success for mutating Dab1 serines at positions 260, 400, 481, 491, and 515 to alanine, individually and combinatorially, and determining the serine(s) that is/are phosphorylated by Cdk5 using the methodology of Niethammer and Keshvara because of the results of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851. Alternatively, one of ordinary skill in the art would have had a reasonable expectation at the time of the invention to combine the teachings of Curran, Keshvara, and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to determine its potential site(s) of phosphorylation according to the method of Carr. Therefore, claims 4-8 and 36-37, drawn to methods for detecting Cdk5 activity would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO ARGUMENT: Beginning at p. 8 of the remarks filed on 4/17/08, applicant argues:

> Applicants respectfully disagree. The present invention is based on the discovery that Dabl is specifically phosphorylated by Cdk5. Before the present invention, a substrate that is selectively phosphorylated by Cdk5 had not been identified. As discussed in more detail above, Niethammer suggests serines 491 and 515 as potential sites for cdk (not just Cdk5) activity. Until Applicants showed in the present invention that Dab 1 is an *in vivo* target of Cdk5, one could not have known or predicted that certain sites in Dabl would only be phosphorylated by Cdk5. Nor does the prior art suggest which serines of Dabl, serines within a candidate sequence (serines 491 and 515), would be a specific target of Cdk5 activity.
>
> Although Curran teaches that Dab 1 is phosphorylated by Cdk5 activity in vitro, there is no suggestion in this reference or other prior art references that Cdk5 phosphorylates Dabl in a biological sample. It is well known in the art that many proteins act as substrates in *in vitro* phosphorylation assays which are not *in vivo* targets for the kinase used in the assay and are not biological targets. Curran only

suggests screening for inhibitors and agonists of *in vitro* phosphorylation of Dabl in connection with reelin binding to VLDLR. Curran does not suggest screening for inhibitors and agonists of *in vivo* Dab 1 phosphorylation by Cdk5.

Ohshima et. al. (PNAS Vol. 98, No. 5, 2764-2769, 2001, reference AK2 in the information disclosure) teaches on page 2768, second column: Although *in vitro* studies indicate that serine/threonine residues(s) of Dab 1 can be phosphorylated by Cdk5/p35 kinase, there is no evidence that Cdk5/p35 phosphorylates Dabl *in vivo*. It has been shown that the Reelin-induced phosphorylation of tyrosine residue(s) of Dab 1 is essential for its function. However, the significance of the phosphorylation of serine/threonine residue(s) remains to be investigated. Our present studies indicate the possibility of interactions of Cdk5/p35 kinase and Reelin/Dabl either in signaling pathways or in indirect regulation of common targets." Thus, the prior art teaches away from direct phosphorylation of Dab 1 by Cdk5 in a biological sample by suggesting the interaction between Cdk5 and Dabl is via a signaling pathway or indirect regulation.

Niethammer makes no suggestion of Cdk5 phosphorylation of Dabl in a biological sample when on page 705, second column, in the paragraph headed "Discussion", it is stated there are three pathways that control neuronal migration. One through reelin by phosphorylation of Dab 1, another through Cdk5 and a third through LIS 1 and PAF. Nothing in this reference suggests that Dab 1 is phosphorylated by Cdk5 in a biological sample.

Keshvara teaches *in vitro and in vivo* methods for identifying Dab 1 phosphorylation by Src. However, there is nothing in Keshvara, Curran or Niethammer to suggest Dabl phosphorylation by Cdk5 *in vivo*. As discussed above, it is well known in the art that many proteins act as substrates in *in vitro* phosphorylation assays which are not *in vivo* substrates for that kinase.

On page 707 column 2 of Niethammer, under the heading "NUDEL Is a Phosphoprotein", it is stated that NUDEL has five consensus Cdk (Not Cdk5) phosphorylation motifs. This reference continues with "It is phosphorylated by Cdk5 *in vitro* and in cotransfected cells. Mutagenesis studies suggest that among the five Cdk5 sites, the first three are likely to be phosphorylated by Cdk5." Furthermore, as discussed above and acknowledged by the Examiner, Niethammer describes Cdk5 phosphorylation sites as a serine or threonine followed by a proline. It does not suggest the candidate sequence of the present invention, a serine followed by a proline in the +1 position and a lysine in the +3 position. Therefore Niethammer fails to teach the identity of the "candidate sequence" of the present invention. Furthermore, Niethammer leaves open the possibility of phosphorylation of other kinases on its Cdk phosphorylation sites. Niethammer does not provide substrate sites that indicate specific Cdk5 activity.

Since Niethammer does not teach a "candidate sequence" as claimed, one could not identify serines 491 or 515 as serines within a candidate sequence by visual

inspection of the amino acid sequences of Gen Bank Accession Number 1771281 and 3288851.

Applicant's argument is not found persuasive. Initially, it is noted that applicant's remarks primarily address the instant rejection by arguing against the references individually, rather than as a combination. To the extent applicant's arguments address the references individually, it is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that the references fail to disclose Cdk5 phosphorylation of Dab1 *in vivo,* it is noted that absence of such an explicit teaching in the prior art would not have taught away from practicing the claimed invention. For example, Niethammer teaches NUDEL is an *in vitro* target of Cdk5, which prompts further analysis to determine if NUDEL is an *in vivo* physiological substrate of Cdk5 (p. 703, column 2 to p. 705, column 1).

Also, while the examiner acknowledges applicant's remark that "many proteins act as substrates in *in vitro* phosphorylation assays which are not *in vivo* targets", it is noted that there appears to be no evidence of record that would suggest that *in vivo* phosphorylation of Dab1 by Cdk5 would not occur. In this case, an ordinarily skilled artisan would have equally recognized that Dab1 could be an *in vivo* target of Cdk5 phosphorylation, particularly in view of the teachings of Niethammer as noted above. Contrary to applicant's position, the prior art's teaching that Dab1 is phosphorylated by Cd5 *in vitro* (see Curran, Ohshima, cited as reference AK2 in the IDS filed on 3/25/02,

and Homayouni, cited as reference AE2 in the IDS filed on 3/25/02) and the absence of an explicit teaching of *in vivo* Dab1 phosphorylation by Cdk5, in combination with the potential biological relevance and importance of Dab1 phosphorylation by Cdk5 as taught by Curran, would have strongly motivated one of ordinary skill in the art to combine the teachings of Curran, Niethammer, Keshvara, and GenBank Accession Numbers 1771281 and 3288851 to immunoprecipitate Dab1 from mouse brain extract with and without catalytically active Cdk5 and analyze its electrophoretic mobility and to determine whether or not serine at position 260, 400, 481, 491, and 515 are phosphorylated by mutating Dab1 serines at positions 260, 400, 481, 491, and 515 to alanine, individually and combinatorially, and determining the serine(s) that is/are phosphorylated by Cdk5 in accordance with the methodology of Niethammer and Keshvara.

Applicant takes the position that the reference of Ohshima, in disclosing that "Although *in vitro* studies indicate that serine/threonine residues(s) of Dab 1 can be phosphorylated by Cdk5/p35 kinase, there is no evidence that Cdk5/p35 phosphorylates Dabl *in vivo*. It has been shown that the Reelin-induced phosphorylation of tyrosine residue(s) of Dab 1 is essential for its function. However, the significance of the phosphorylation of serine/threonine residue(s) remains to be investigated. Our present studies indicate the possibility of interactions of Cdk5/p35 kinase and Reelin/Dabl either in signaling pathways or in indirect regulation of common targets" teaches away from "direct phosphorylation of Dab1 by Cdk5 in a biological sample". However, this appears to be applicant's own interpretation of the statement by Ohshima. In this case, Ohshima

does not appear to explicitly or implicitly state that Dab1 is not directly phosphorylated by Cdk5 and thus, applicant's interpretation appears to be based solely on arguments of counsel. Since Ohshima teaches the possibility of "interactions of Cdk5/p35 kinase and Reelin/Dabl either in signaling pathways", the noted statement would appear to equally or preferably be interpreted by an ordinarily skilled artisan as meaning that Cdk5/p35 kinase and Reelin/Dab1 interact directly in a phosphorylation signaling pathway. That this interpretation would equally or preferably be applied to the statement of Ohshima is suggested by Ohshima's disclosed teaching of *in vitro* phosphorylation of Dab1 by Cdk5. Moreover, at least in view of the teachings of Curran, *i.e.,* that "identification of the site of Dab1 phosphorylation may permit its use as a potential target for agonists and antagonists. Cdk5 phosphorylates Dab1 in vitro...Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. Thus, this area of exploration has significant relevance" (column 23, line 63 to column 24, line 4), one would have been motivated to identify the site(s) of Dab1 phosphorylation by Cdk5 both *in vitro* and *in vivo*.

Addressing the reference of Niethammer, it appears applicant takes the position that since Niethammer fails to identify "the candidate sequence of the present invention, a serine followed by a proline in the +1 position and lysine in the +3 position" that the reference fails to identity *the* candidate sequence of the invention, leaves open the possibility of phosphorylation of other kinases on its Cdk phosphorylation sites, and does not provide substrate sites that indicate specific Cdk5 activity. However, as noted above, Niethammer points out those Cdk5 consensus phosphorylation sites of NUDEL

as being S-P or T-P (p. 703, column 2, bottom and p. 698, Figure 1A), which are present in Dab1 as evidenced by GenBank Accession Numbers 1771281 and 3288851, and neither Niethammer nor any other cited reference teaches away from applying the same method to identifying the site(s) of Dab1 phosphorylation by Cdk5 *in vivo*.

Thus, at least for the reasons stated above, the examiner maintains the position that the combination of cited references properly establishes a *prima facie* case of obviousness.

[10] The rejection of claim(s) 10-11, 13-15, and 38 under 35 U.S.C. 103(a) as being unpatentable over Curran in view of Keshvara, Niethammer, Carr, and GenBank Accession Numbers 1771281 and 3288851 as applied to claims 4-8 and 36-37 above and further in view of Howell et al. (*Genes Develop.* 13:633-648, 1999; cited as reference AY1 in the IDS filed on 3/25/02; "Howell"), Fu et al. (*Nature Neurosci.* 4:374-381; "Fu"), Michalewski et al. (*Analytical Biochem.* 276:254-257, 1999; "Michalewski"), and Zhen et al. (*J. Neurosci.* 21:9160-9167, 2001; "Zhen").

The claims are drawn to methods of detecting Cdk5 serine kinase activity in a biological sample, by determining whether Dab1 is phosphorylated on a serine residue. The claims limit the method of detection of Dab1 phosphorylation to using an antibody that binds to Dab1 only when it is phosphorylated on serine or to an antibody generated against SEQ ID NO:3.

The references of Curran, Niethammer, Keshvara, Carr, and GenBank Accession Numbers 1771281 and 3288851 disclose the teachings as set forth above. The

combination of references does not appear to teach or suggest using a phosphoserine antibody, optionally against SEQ ID NO:3, in the methods disclosed therein.

As noted above, at the time of the invention, methods for analyzing protein phosphorylation were well known in the art. Particularly well-known were methods for analyzing phosphorylation of a polypeptide using antiphosphoamino acid antibodies. See particularly Michalewski, which teaches a polyclonal antiphosphoserine antibody (p. 254, column 2, middle) and Zhen, which teaches a monoclonal antiphosphoserine antibody (p. 9161, column 2, middle).

Howell teaches a method for analyzing *in vivo* and *in vitro* Dab1 tyrosine phosphorylation using an anti-tyrosine antibody (p. 645, Figures 2-3 and p. 646, Figure 4).

Fu teaches a method for analyzing Cdk5 serine phosphorylation of ErbB3 using an anti-phosphoserine antibody (p. 377, Figure 5; p. 379 under "*Chemicals and antibodies*; and p. 380 under In vitro *phosphorylation assay*).

Therefore, at the time of the invention it would have been obvious to one of ordinary skill in the art to combine the teachings of Curran, Niethammer, Keshvara, GenBank Accession Numbers 1771281 and 3288851, Howell, Fu, Michalewski, and Zhen to analyze the phosphorylation of mouse or human Dab 1 at positions 260, 400, 481, 491, and 515 by using a monoclonal or polyclonal anti-phosphoserine antibody. While it is acknowledged that the prior art does not teach or suggest the use of an anti-phosphoserine antibody against SEQ ID NO:3 herein as recited in claims 11, 32, 35, and 38, it is noted that such an antibody is viewed as a "product-by-process"-type

limitation. According to MPEP 2113, "'[i]f the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.' *In re Thorpe,* 777 F.2d 695,698,227 USPQ 964,966 (Fed. Cir. 1985)... Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi,* 710 F.2d 798,802,218 USPQ 289,292 (Fed. Cir. 1983). One would have been motivated to do this because Curran expressly teaches that Cdk5 phosphorylates serines of Dab1 and the sites of Cdk5 phosphorylation of Dab1 can be identified and exploited to screen for agonists and antagonists as described above and the use of an anti-phosphoserine antibody to detect phosphoserine avoids of the use of radioactivity. One would have had a reasonable expectation of success to analyze the phosphorylation of mouse or human Dab 1 at positions 260, 400, 481, 491, and 515 by using an anti-phosphoserine antibody because of the results of Curran, Niethammer, Keshvara, GenBank Accession Numbers 1771281 and 3288851, Howell, Fu, Michalewski, and Zhen. Therefore, claims 10-11, 13-15, and 38, drawn to methods for detecting Cdk5 activity would have been obvious to one of ordinary skill in the art at the time of the invention.

RESPONSE TO ARGUMENT: Beginning at p. 10 of the remarks filed on 4/17/08, applicant argues:

> For the reasons stated above, there is nothing in the prior art references of Curran, Keshvara, Niethammer and the recited GenBank Accession Numbers to suggest the inventions in claims 6-8 and 36-37. Thus combining Howell, Fu, Michalewski and Zhen with Curran, Keshvara, Niethammer and the recited GenBank numbers does not render the antibodies of claims 10 - 11, 13 -14 and 38 obvious.

Applicant's argument is not found persuasive. At least for the reasons stated above, the examiner maintains the position that the combination of cited references properly establishes a *prima facie* case of obviousness.

Conclusion

[11] Status of the claims:

Claims 4-8, 10-11, 13-15, and 36-38 are pending.

Claims 4-8, 10-11, 13-15, and 36-38 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
David J. Steadman, Ph.D.

Primary Examiner
Art Unit 1656